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Interictal infraslow activity in patients with epilepsy

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HIGHLIGHTS

- Interictal infraslow activity (ISA) can provide additional information about the epileptogenic process.
- It can be assessed with conventional EEG systems.
- ISA activity is more widely distributed in localisation-related epilepsies than might be assumed.

ABSTRACT

Objective: To evaluate if interictal infraslow activity (ISA), as obtained from a conventional EEG system, can contribute information about the epileptogenic process.
Methods: The entire long-term intracranial monitoring sessions of 12 consecutive patients were evaluated on an XLTEK system for ISA. Three additional patients had long-term scalp recordings.
Results: In intracranial as well as scalp recordings, the ISA background was consistently higher in the waking state than during sleep. From this background emerged intermittently focal changes, which could achieve in intracranial recordings millivolt amplitudes, while they remained in the microvolt range in scalp recordings. Although they were mainly contiguous between adjacent channels, this was not necessarily the case and intermittent build-up could be seen distant from the epileptogenic zone or radiographic lesion.
Conclusions: Interictal ISA can be detected in routine intracranial and scalp recordings, without the need for DC amplifiers, and can provide additional information.
Significance: Since ISA is a separate element of the electromagnetic spectrum, apparently non-neuronal in origin, its assessment should be included not only in the pre-surgical evaluation of epilepsy patients but also in patients with other neurologic disorders and normal volunteers.

1. Introduction

The change from analogue to digital EEG systems and associated improvements in amplifier technology has opened new vistas for the exploration of cerebral electrical activity. Frequencies above the gamma band which previously required for visualisation of films from cathode-ray oscillograph tracings or tape recordings which manipulated data acquisition and playback speeds (Buchwald et al., 1966; Buchwald and Grover, 1970; Rodin et al., 1971a,b, 1977; Rodin and Wasson, 1973; Rodin, 1972, 2005), can now be readily observed in routine clinical recordings when high sampling rates are employed. This frequency range is currently under intense investigation and only some early as well as the latest references will be listed (Allen et al., 1992; Fisher et al., 1992; Bragin et al., 1999; Worrell et al., 2008; Jiruska and Bragin, 2011; Modur et al., 2011, 2012; Wang et al., 2013).

A similar situation pertains to the recording of <0.5 Hz activity. These frequencies had previously required DC amplifiers for display but currently all commercial EEG systems have a lower frequency limit of at least 0.1 Hz, while it is 0.05 Hz for the XLTEK system and 0.016 for the Nihon-Kohden system. Since the signals below these frequencies are not abolished but merely attenuated in amplitude and wave duration, even slower activity is retrievable from routinely obtained clinical data.

Early publications have shown that epileptic seizures can be associated with slow baseline shifts, which can have localising significance (Cohn, 1954; O'Leary and Goldring, 1959; Vanasupa et al., 1959; Gumnit and Takahashi, 1965; Caspers and Simmich, 1966; Chatrian et al., 1968; Gumnit et al., 1970). Inasmuch as these observations required DC amplifiers, they were referred to as 'DC shifts'. Yet Ikeda et al. demonstrated that these shifts were also observed, in intracranial as well as scalp recordings, when conventional

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AC amplifiers with a long time constant were used (Ikeda et al., 1996, 1999). The finding was subsequently verified by several other investigators (Gross et al., 1999; Thordstein et al., 2005; Bragin et al., 2005; Mader et al., 2005; Hughes et al., 2005; Rodin et al., 2006, 2008, 2009; Rodin and Modur, 2008; Ren et al., 2011; Shi et al., 2012; Rampp and Stefan, 2012; Constantino and Rodin, 2012; Modur et al., 2012).

Most of these studies also showed that ictal baseline shifts were not unidirectional but consisted of a series of high-amplitude slow waves of varying durations, involving at times a large number of channels at different time points during the seizure and extending into the post-ictal period. The latter aspect was most marked in the immediate post-ictal state after a tonic–clonic seizure when the conventional EEG frequencies showed attenuation. Figures 6 and 7 of the publication by Rodin and Modur (2008) provided a typical example. When one keeps these observations in mind, two aspects become apparent. One is that the terms 'baseline shifts' or 'DC shifts' are inadequate to describe the phenomenon because one is dealing with a marked increase of continually present infraslow activity (ISA). The other aspect is that ISA follows different laws and therefore must have different generators than the conventionally sampled frequency band.

As mentioned earlier, there are by now several studies which deal with the ictal aspects of ISA, but a review of the literature showed that there appeared to be no publications specifically devoted to the pre- and interictal state in epilepsy patients. Yet, this information could potentially also be important especially with regard to seizure prediction, which is still imprecise. We, therefore, decided to study this problem in a systematic prospective manner. A preliminary report was presented at a symposium on cerebral electromagnetic ISA of the American Clinical Neurophysiology Society and subsequently published (Rodin and Funke, 2012; Constantino and Rodin, 2012). Since the patient number was small and there were no data available on scalp recordings monitored over the long term, the study was continued on a larger patient population which also included scalp recordings.

The questions to be answered were: (a) Does interictal ISA contain additional information which is not readily available from the conventional frequency band? (b) If this were to be the case, does it have potential clinical relevance with regard to the patient's seizure disorder? (c) Can interictal, and especially pre-ictal, ISA contribute to the prediction of the occurrence of a seizure?

2. Materials and methods

The methodology was the same as in the previous report (Constantino and Rodin, 2012) but seven additional patients with intracranial and three with scalp recordings were added. Of these 12 patients with intracranial data, 11 also had scalp recordings at our laboratory. However, these had been obtained earlier and contained only samples rather than the complete monitored sessions. The samples consisted, apart from seizures, of an initial 35-min epoch, subsequent 35-min samples of what the XLTEK program regarded as an "event" and hourly 1-min epochs of interictal data. The three new patients with long-term scalp recording sessions have not yet had further intracranial investigations. The clinical characteristics of the patients are shown in Table 1. It should be emphasised that the study was prospective and contained all patients who had been recorded between August 2011 and February 2013.

Scalp, as well as intracranial, recordings were obtained on an XLTEK system. For scalp recordings, EMU40 amplifiers were used (40 channels; low-frequency cut-off at 0.05 Hz–6 db/octave), while the intracranial data were recorded with 128SF amplifiers (128 channels; low-frequency cut-off at 0.03 Hz–6 db/octave). After de-identification, the data were transferred to an external drive before they were sampled for storage purposes. For intracranial recordings, the sampling rate was 512 Hz while it was 256 Hz for scalp recordings. The intracranial strip and grid electrodes were platinum (Ad-Tech Medical Instruments, Racine, WI, USA) and for scalp recordings Ag/AgCl electrodes were used. For intracranial recordings, the electrode coverage ranged from 20 to 88 electrodes and, except for two cases, was unilateral in areas of suspected seizure origin. The scalp electrodes were placed according to the 10/20 system but infraorbital and at times T1/T2 and/or sphenoidal electrodes were added. For intracranial recordings, the reference electrode was a needle electrode inserted into the temporalis muscle.

For data analysis, the software package BESA® (BESA Research version 6; BESA GmbH, Gräfelfing, Germany) was used. Initially, the data were reviewed on the conventional frequency band (0.5–70 Hz), and when muscle artefact contaminated the scalp recordings, the low-pass filter was set to 15 Hz. The program allowed for removal of eye blinks as well as lateral eye movements and this module was used when indicated. For better visualisation

Table 1
Clinical profile of patients.

Patient	Age/sex	MRI	Resection performed	Latest operative result
1	48/F	Cerebellar atrophy and white matter changes	L A T lobectomy with hippocampectomy	Seizure free since surgery 9/2011
2	20/F	Normal	R A T lobectomy with hippocampectomy	Seizure free since surgery 8/2011
3	33/M	Previous L T lobectomy	L STG resection	Seizure free since surgery 9/2011
4	32/F	L F encephalomalacia; multiple cav mal	L insular cav mal lesionectomy	Seizure free since surgery 10/2011
5	29/M	Small L hemisphere and hippocampus	L A T lobectomy with hippocampectomy	Seizure free since surgery 11/2011
6	54/M	Multple cav mal; bifrontal encephalomalacia	R insular cav mal lesionectomy	Seizure free since surgery 01/2012
7	49/M	Normal	R A T lobectomy with hippocampectomy	Seizure free since surgery 02/2012
8	32/M	R F encephalomalacia	Partial R F lobe resection	1 seizure since surgery 5/2012
9	23/F	R F encephalomalacia	R F lobe resection	Occasional seizures
10	41/M	Normal	None[b]	N/A
11	32/F	Normal	R T lobectomy	Died of SUDEP after surgery
12	13/F	L T dysplasia	L T lobectomy (Frontal focus not resected)	Still having seizures
13[a]	24/M	Normal	None[b]	N/A
14[a]	48/F	L parahippocampal hemosiderin c/w trauma	None[b]	N/A
15[a]	20/F	L P tumor resected; additional mass L F and L T	None[b]	N/A

All patients had temporal seizure semiology; R, right; L, left; F, frontal; P, parietal; T, Temporal; STG, superior temporal gyrus; Cav mal, cavernous mal formations.
[a] Scalp EEG only.
[b] No surgery was performed in 10 due to discordant Wada, 13 was controlled with medications, 14 had strong memory on the lesion side, and 15 had additional tumor in anatomically critical areas.

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of pre-ictal scalp activity, a variety of montages were used which included bipolar, referential and average common reference. For intracranial recordings, the reference electrode proved unsatisfactory and the data were, therefore, transformed to an average common reference of artefact-free channels as well as, at times, a bipolar montage of adjacent electrodes. After removal of the high-pass filter, the data were subsequently downsampled to 10 Hz for an effective upper frequency of 3.3 Hz in order to assess ISA. For its evaluation, the high-pass filter was left open and the low-pass filter set to 0.1 Hz (forward, 6 db/octave). This yielded pure ISA and it was viewed on windows ranging from 5 to 20 min, which is the current limit of the program. For evaluation of possible pre-ictal changes in the data, the FFT module was used on unfiltered raw data for varying epochs and different frequency bands.

The monitoring sessions for archived scalp recordings lasted from 2 to 6 days. For the three patients with continued scalp recordings, they ranged from 2 to 7 days. The intracranial sessions lasted from 2 to 8 days, with one outlier of 16 days. The sampled scalp recordings contained 20 partial and four secondarily generalised seizures, while during the continuously monitored recordings, four partial seizures had occurred and an additional one became tonic–clonic after partial onset. Since the waking scalp recordings were frequently contaminated by a variety of artefacts, only those seizures which arose from sleep were evaluated for pre-ictal changes. This reduced the number to three partial seizures and one secondarily generalised one. For the intracranial recordings, no selection was needed and the data contained 33 partial and three secondarily generalised seizures. The clinical characteristics of the patients are shown in Table 1.

3. Results

3.1. Intracranial data

Interictal ISA was characterised by background activity, which differed in amplitude and frequencies over time within a given channel as well as among the various sampled brain regions. Intracranial recordings did not allow a differentiation of sleep stages and the resting eyes-closed state, on the video recording, could not be distinguished from sleep. Therefore, two active waking conditions, e.g., during eating and/or some other activity, were compared with two sleep epochs: around 2 a.m. and prior to awakening in the morning. The maximal ISA background frequency power values were: for the waking state 5640 μV^2, for morning sleep 4749 μV^2 and for nocturnal sleep 2240 μV^2. The lowest values were consistently seen during nocturnal sleep. In the patients in whom structural lesions were present, background activity was usually highest in the vicinity of the lesion but these

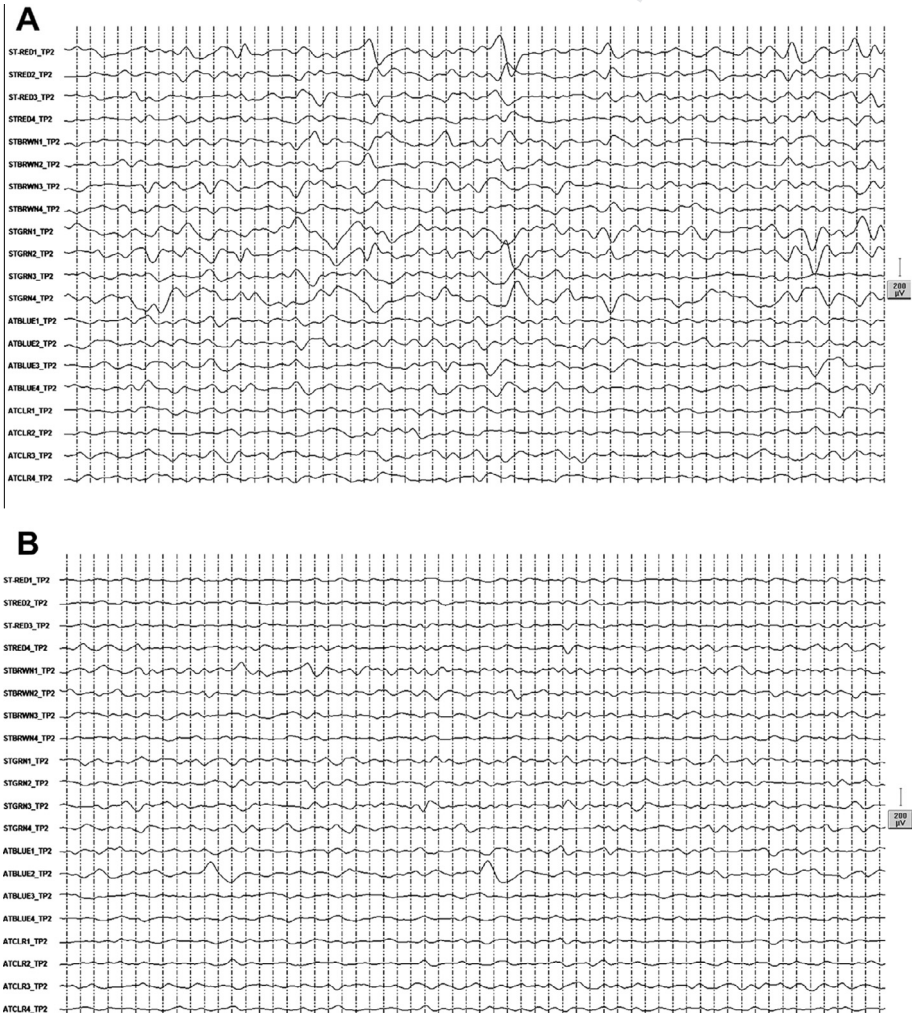

Fig. 1. 10 min sample of intracranial interictal ISA background from patient 10. Top (A) shows the waking state, bottom (B) nocturnal sleep. Calibration bar 200 µV, vertical bars delineate 10 s. The tracings are artefact free and the amplitude reduction during sleep is apparent. In all figures, an average common reference montage was used.

Table 2
Relationship of spike and seizure onset location to ISA and intracranial recordings.

Patient#	Scalp			Intracranial		
	Spikes	Seizure onset	ISA	Spikes	Seizure onset	ISA
1	BiT L>R	LT	BiT L>R; LF	LT; LF	LT	LT; LF
2		NA		RT	RT	RT
3	BiT L>R	LT	BiT	LT; LF	LT	LT
4	BiT L>R; LF	T	BiT	LT; LF	LT; LF	LT; LF
5	LT	LT	BiT L>R; LF	LT; LF	LT	LT; LF
6	BiT R>L	RT?	BiT	RT	RT	RT; RF
7	BiF; RT	RF	BiFT	RF; LT	RF; LT?	RF; LT
8	RT	RT?	BiT R>L; RF	RF; LT	RF; LT?	RF; RT
9	RT; RF	RT?	BiT R>L; BiF	RF; LT	RF; LT?	RF; RT
10	LT	LT	BiT L>R	LT; RF	LT; RF	LT; RT; RF
11	RT; LF	RT?	BiT L>R, FPZ	RT	RT	RT; RF
12	BiT L>R	LT, LC	BiT L>R; LF	LT	LT; LF	LT; LF
13	LT; RF	LT	LF, RT		NA	
14	BiT L>R	LT?	LT, LF, RT		NA	
15	LT	LCTP	LT, RF, RT		NA	

Bi, bilateral; R, right; L, left; T, temporal; F, frontal.

electrodes were not necessarily identical with those from which seizure onset had been recorded.

A typical 10-min sample of raw data for the waking state and during nocturnal sleep is shown in Fig. 1 from patient 10. In this figure, as well as all others, a common average reference was used and for ISA only downsampled data are shown. Initially, this patient had bilateral implants of subdural strips which recorded from frontal and temporal areas (48 channels), but the implant was subsequently revised to cover the left temporal area in greater detail with 20 channels. The top portion of the figure (A) represents the background activity while the patient was eating breakfast and the lower portion (B) shows nocturnal sleep. In this, and all other

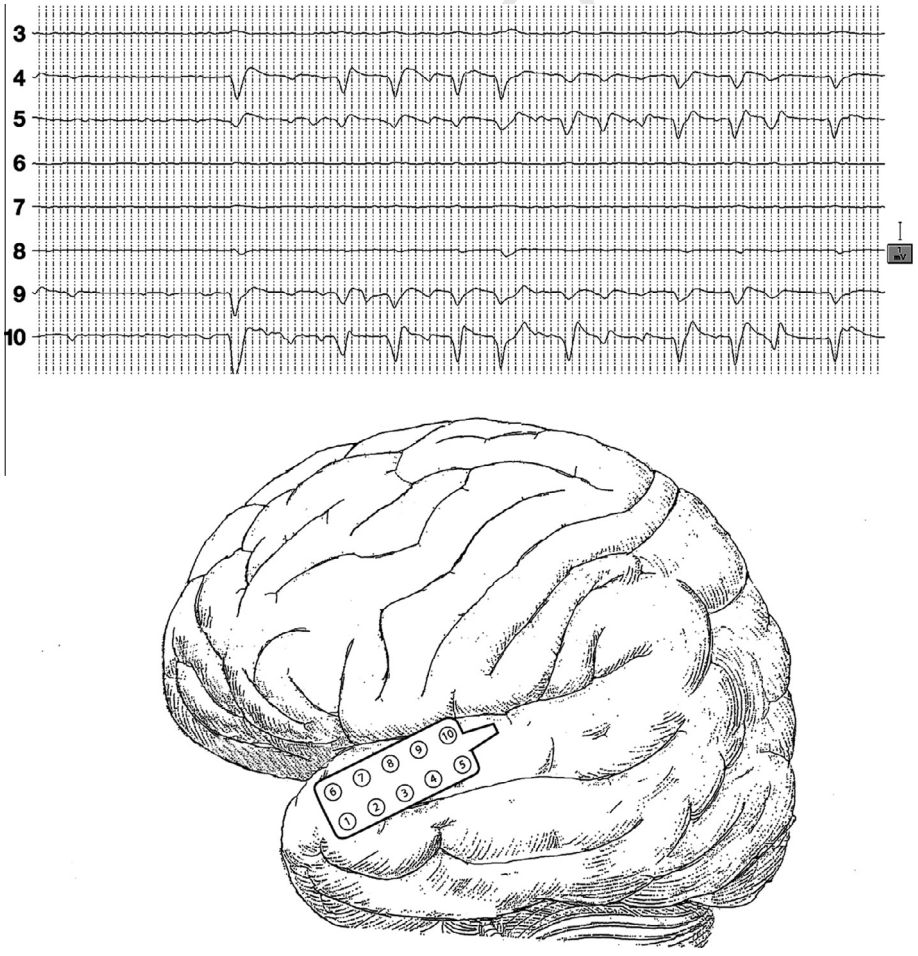

Fig. 2. 20 min example of increased focal temporal ISA from patient 1 (average common reference). The activity lasted four and a half hours and is contiguous for contacts 4–5 and 9–10 of a 2 × 5 strip. The calibration bar reflects 1 mV. Electrodes 1 and 2 of the strip did not show activity and were omitted from the figure. The strip location is shown on the bottom of the figure.

pictures which deal with ISA, the vertical bars reflect 10-s intervals, while for data of 60 s or less they reflect 1-s intervals. Amplifications were held constant at 200 μV in order to demonstrate more clearly the difference between these two states. The FFT values for these segments will be shown later in conjunction with scalp-recorded data.

An overview of the relationship of the location of spike discharges, seizure onset and ISA is shown in Table 2, which also includes the scalp-recorded data. In patients 2 and 3, only temporal lobe structures were covered by electrode strips, while in the rest of the patients, frontal strips and/or grids were also available. In only two instances, patients 7 and 10, had the electrode strips been placed bilaterally. Although the data showed good agreement between spikes, seizure onset and ISA, this lobar assessment masked differences within a given lobe for the individual electrodes which were involved. The most prominent ISA was usually in the vicinity of the area which displayed the most marked activity on conventional frequencies but was not necessarily recorded from the same electrodes which had shown maximal spiking and/or seizure onset.

From this background emerged intermittently higher-amplitude discharges which could be limited to one electrode, covered several electrodes of strips/grids or involved, at times, all sampled areas with different amplitudes at different locations. When only a single electrode was involved, it usually represented a momentary electrode artefact. However, this became unlikely when several neighbouring electrodes of one strip were involved as shown in Fig. 2 (patient 1). The maximum amplitude of this activity was 2.8 mV. It lasted for 4.5 h. Prolonged discharges of this type were most commonly seen in the morning hours prior to awakening and extended into next day's file, which started around 7 a.m.

The amplitudes of prolonged interictal discharges ranged from about 400 μV to several millivolts and could, at times, exceed those which were seen during the ictal state of partial seizures. Furthermore, although contiguity between neighbouring electrodes was clearly present in some instances, as shown in Fig. 2, in other instances, neighbouring electrodes were skipped and the activity was present at some distance from the patient's lesion as shown in Fig. 3A and B (patient 6). Fig. 3C shows the location of the grid and a coronal MRI view of the lesion.

ISA increase did not only appear in the ictal onset zone, but also in distant areas of a separate lobe and in the contralateral hemisphere. Patients 8 and 9 are of special interest because they had encephalomalacia in the frontal lobe. Intracranial seizure onset was likewise observed in the frontal lobe but episodic ISA increase was additionally seen in the temporal lobe.

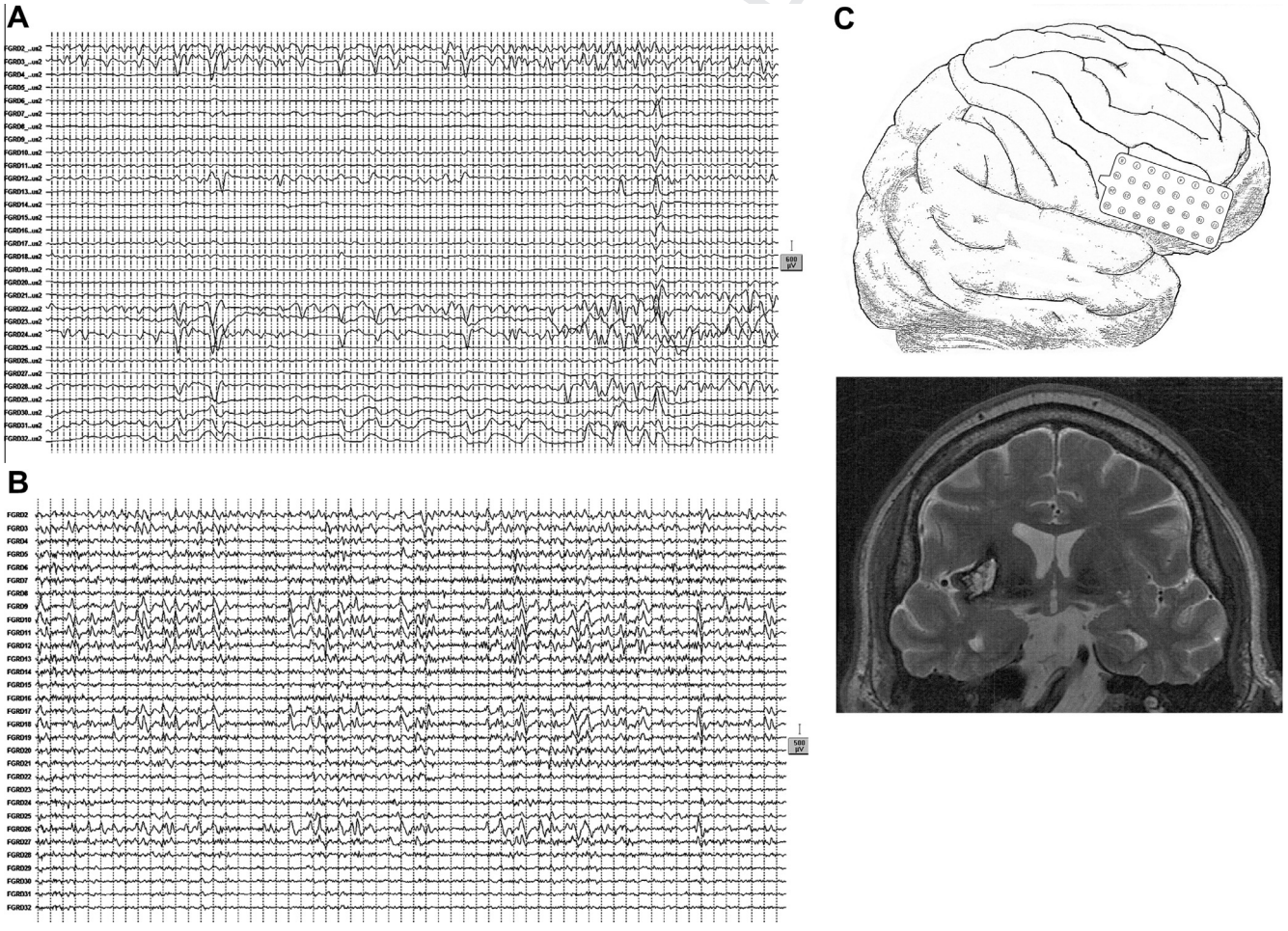

Fig. 3. (A and B) Example of contiguity as well as dis-contiguity of ISA buildup in a prefrontal 8 × 4 grid from patient 6. Portion (A) shows 20 min of ISA buildup, and (B) shows one min on conventional filter settings. Calibration bar reflects 500 μV for both segments but the vertical bars in section B reflect 1 s intervals. ISA buildup differs from what is seen in conventional frequencies. Electrode 1 of the grid was removed because of artefact. Please note also that electrode contacts 2 and 3 of the grid, although contiguous, are far removed from the lesion location and distant from the other contiguous electrode activity at 22–24 and 28–32. (C) The top portion shows the grid location and the bottom portion a coronal MRI view of the lesion. Additional strips in the Sylvian area and the temporal lobe, which did not participate in this particular discharge, were omitted from the diagram.

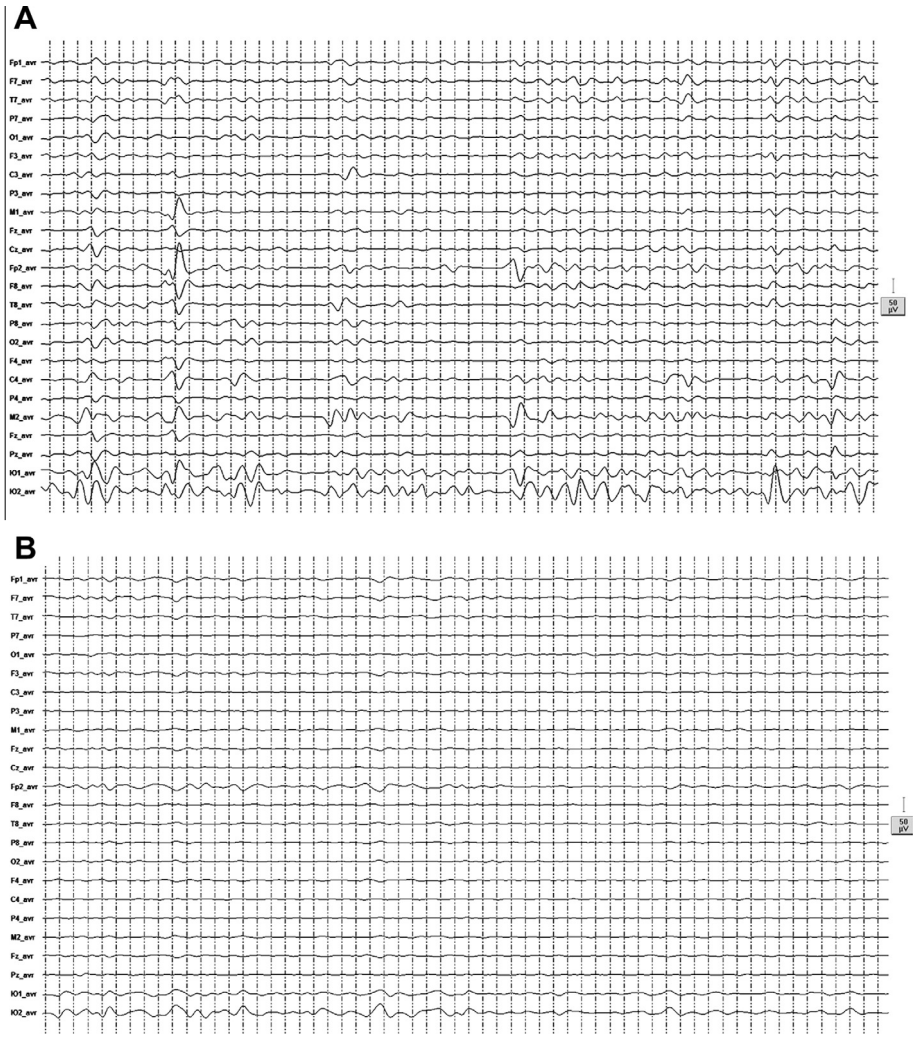

Fig. 4. 10 min scalp recorded sample of interictal ISA background from patient 14. Calibration bar 50 μV, vertical bars delineate 10 s. Top (A) shows the waking state and the bottom segment (B) nocturnal sleep. The tracings are artefact free and the ISA amplitude reduction during sleep is again apparent.

3.2. Scalp recordings

Long-term scalp recordings have the advantage of covering a larger number of brain areas and are useful in selecting the region(s) for implantation of intracranial electrodes. However, ISA recordings from the scalp have the distinct disadvantage of being subject to considerably more artefacts than intracranial data. Although the BESA program has a module which can eliminate most eye blinks and to some extent lateral eye movements, maps of the corrected data still showed, on occasion, the typical pattern associated with lateral eye movements. In addition, other-movement artefact is a major problem. In the three patients who had long-term recordings spanning from 2 to 7 days, it was noted that the patients' sleep only rarely reached stage IV for brief periods and the V-wave, spindle, K-complex stages were frequently interrupted by shifts in position of the patient with concomitant movement artefact. A typical picture of an artefact-free 10-min waking and sleep epoch is shown in Fig. 4 (patient 14). Similar to the intracranial data in Fig. 1, the decrease in amplitude during sleep is apparent.

ISA power was greater in waking than in sleep and greater from implanted electrodes than from scalp recordings. Fig. 5 shows the FFT power values for patient 14 as well as subdural electrodes from patient 10 whose raw data were presented in Fig. 1. Longer duration build-up of ISA was seen in various regions but was usually bilateral and since even sleep was disrupted by movement artefact not all of the findings were trustworthy. Nevertheless, occasionally a reliable focal build-up was recorded which would have been missed had only the conventional frequency band with a short time window of about 20 s been used as Fig. 6 demonstrates. Fig. 7 shows that when one enlarges the viewing window to 3 min, which is about the maximum before the data are too compressed for accurate assessment, focal activity emerges.

This was not a unique event because a similar one from the right frontotemporal region was observed in patient 15 as shown in Fig. 8. This finding is especially noteworthy for two reasons. One is that in contrast to patient 14 where the build-up occurred on the side of seizure onset, although more posterior, in the temporal area, it appeared on the contralateral side in this case. The second one is that the patient did have a left parietal partially resected astrocytoma. Two partial seizures were observed during the monitoring sessions and both originated in the left hemisphere, the central area in one and the temporal area in the other. Patient 13 also showed intermittent build-up in the temporal regions but for <20 min and in a bilaterally independent manner.

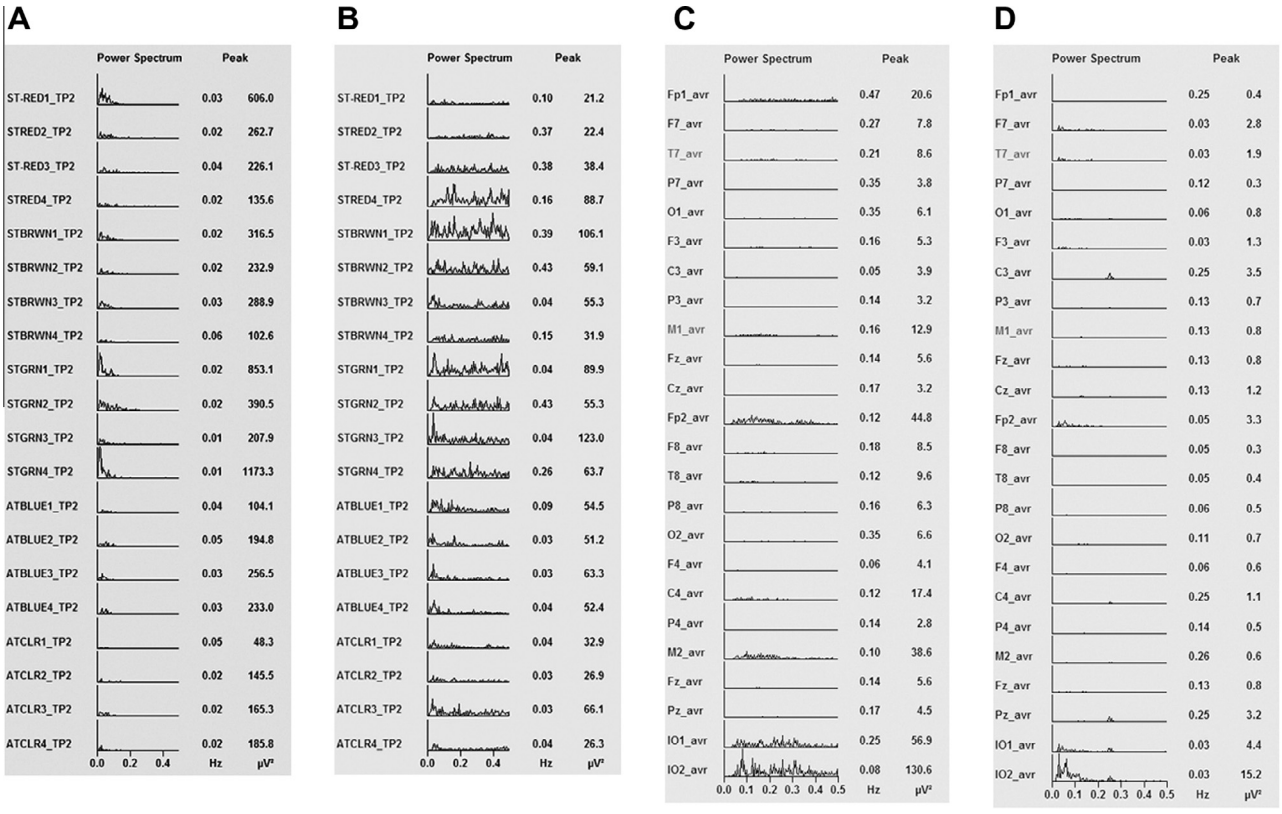

Fig. 5. Comparison of power spectra for the waking and sleeping state in intracranial and scalp recordings from patients 10 and 14. Section (A) intracranial waking, section (B), intracranial sleep, section (C) scalp waking, section (D) scalp sleep. The differences between waking and sleep are apparent for both types of recordings and the data also show the expected attenuation of background power in scalp recordings as compared to intracranial ones.

4. Discussion

The data presented here are in full agreement with our preliminary observations (Constantino and Rodin, 2012) and demonstrate what can be expected when ISA is evaluated during long-term monitoring sessions. In addition, the current study extends the information to long-term scalp recordings. Although the current study has some limitations, which will be discussed later, it does lend itself to conclusions which are of value. The most important aspect is that the study confirmed that ISA is a normal part of the cerebral electrical spectrum, which can be accessed without recourse to DC amplifiers. The statement by Vanhatalo et al. (2004) that, "These oscillations (0.02–0.1 Hz) are not detectable in conventional electroencephalography because of its limited recording band width (typical lower limit 0.5 Hz)" and which was repeated, with similar words, in 2005 (Vanhatalo et al., 2005) as well as 2010 (Vanhatalo et al., 2010), is no longer tenable. It was based on analogue EEG systems but these have been replaced by digital equipment with lower-frequency input filters as has been mentioned in Section 1.

It is also of interest to note that even when DC amplifiers were used by the mentioned authors the data were subsequently filtered to a range of 0.02–0.1 Hz. The resultant activity, as shown in Figs. 2A and 3A of the above-mentioned 2004 publication, as well as Fig. 6 of the one of 2005 demonstrate that amplitudes and frequencies are in accord with those which are presented here. Other authors who have used DC amplifiers have also at times restricted their ISA data analysis to the 0.02–0.1 frequency range (Monto et al., 2008). While activity between 0.001 and 0.1 Hz can readily be investigated with conventional EEG systems, the investigation of waveforms lasting longer than about 17 min will require the use of DC amplifiers.

The first two questions asked in Section 1 can now be answered affirmatively. The most important one is that interictal ISA build-up occurs regularly, which is not apparent when only the conventional frequency band, with a short viewing window of 10 or 20 s, is inspected. This fact can readily be observed when the high-pass filter is removed and the viewing window opened to minutes instead of seconds. Furthermore, interictal ISA provides additional information, which may well be of clinical importance.

With regard to the third question raised in Section 1, seizure prediction, the findings are less clear. The fact that ISA build-up has a waxing and waning quality over a 24-h period, which is not directly related to the time of seizure occurrence, may make seizure prediction based on ISA more difficult. When FFTs were obtained in 1-min increments over a 10-min period prior to a given seizure, increase in power was, in general, variable and occasionally even decreased immediately prior to and at the beginning of the seizure. More commonly, however, the minute before the seizure showed power increase, which was further enhanced with seizure onset. An attempt to establish consistent relationships would require statistical evaluations which were beyond the scope of the present study.

The current investigation confirmed that the lowest background ISA occurs during nocturnal sleep, which seems counterintuitive when only the conventional frequency band is considered. However, increase in the waking state and decrease during sleep was also observed with intracranial high-frequency recordings in animals (Rodin and Wasson, 1973). Although stage IV sleep was only achieved for brief periods and the findings shown in the figures represent the spindle and K-complex stages, they are still valid. Brief segments of stage IV sleep were present in patient 15 and FFTs showed the same ISA reduction. It was noted furthermore that

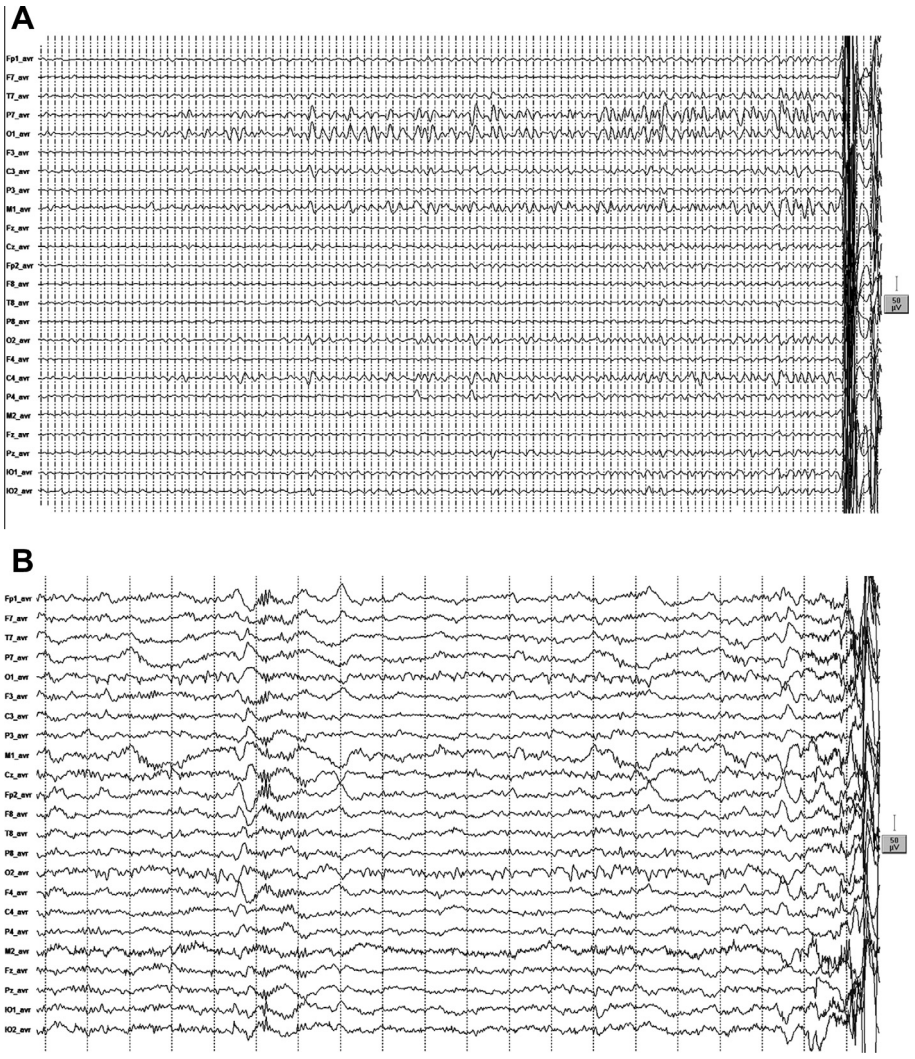

Fig. 6. Example of focal temporal buildup during sleep in a scalp recording (patient 14). Top (A) shows 20 min of ISA with buildup at P7-O1 and later M1 as well as T7. It is also reflected to some extent at C4, P4, O2 and is terminated by a shift in body position. The bottom section (B) demonstrates on a 20 s segment of conventional filter settings just prior to the movement artefact that the focal activity cannot be seen because of normal sleep changes. Calibration bar 50 µV for both sections, vertical bars delineate 10 s for A and 1 s for B.

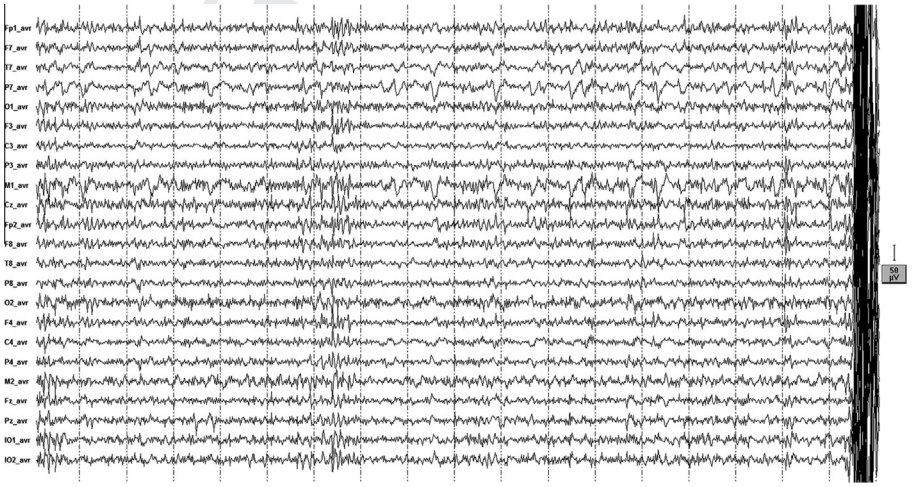

Fig. 7. Same buildup on conventional filter settings but the window was enlarged to cover 3 min. Focal slowing can now be discerned at P7 and M1. Calibration bar 50 µV and the vertical bars reflect 10 s intervals.

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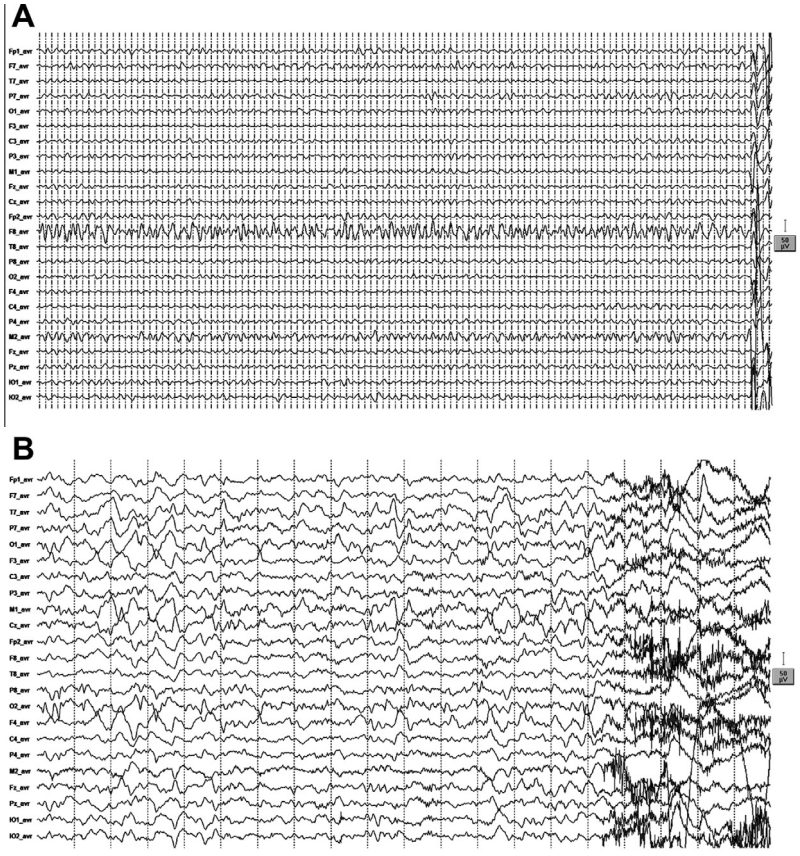

Fig. 8. Similar buildup in patient 15 during sleep. Top section (A) 20 min ISA segment shows rhythmic activity at F8 and M2. It had started 10 min earlier and was again terminated by a body movement. Bottom section (B) demonstrates that 20 s on conventional filter settings fail to show increased focal activity because of normal sleep patterns. Calibration bar shows 50 μV for both segments. Vertical bars at A reflect 10 s intervals and 1 s intervals at B.

when the data were examined separately for the delta band, defined as 1–3 Hz, the values were clustered at the edge of the spectrum at 1 Hz. When the 1 Hz filter was removed and the unfiltered data were examined, the frequencies ranged during the delta stage from 0.07 to 0.7 Hz in different channels. The current delta-frequency band definition with a low-frequency cut-off of either 0.5 or 1 Hz was based on analogue technology, which eliminated the lower frequencies and, therefore, does not necessarily conform to physiological parameters.

The interictal intracranial observations agreed with what had had been previously reported for ictal data. ISA increase does not necessarily appear in the channels which show maximal activity in the conventional frequency band but in neighbouring ones (Rodin and Modur, 2008). A puzzling aspect is, however, that interictal ISA build-up did not only appear in contiguous channels of a grid or strip but also in distant ones, as shown in Fig. 3A, while the activity is contiguous for conventional frequencies (Fig. 3B). This discrepancy suggests that different electrophysiological processes are responsible for these different frequencies.

The study also raised an additional question: can some of the observed ISA build-up, when it occurs in the waking state, be associated with clinical symptoms? In one instance (patient 2) the patient pushed the event button, but as the EEG did not show abnormalities it was regarded as an 'accidental button push'. Yet, ISA had definitely increased for a 5-min period. In another instance (patient 10), the patient's wife reported that his speech did not make sense. High-amplitude 25-min ISA build-up was present at that time but there was no counterpart in the conventional frequencies. Inasmuch as the patients were not constantly observed, by nursing personnel or family, one cannot know to what extent a relationship of this type might have existed in other instances of ISA build-up.

A further aspect needs to be mentioned. In intracranial as well as scalp recordings, one could, at times, see prolonged extremely rhythmic activity at 0.2 or 0.3 Hz at a single electrode. This usually occurred after that electrode had previously shown momentary artefact (typical 'electrode pop') and probably registered respiration rather than cerebral electrical activity as shown in a previous publication (Rodin and Funke, 2006).

Scalp-recorded ISA data can be used only with considerable caution because of unavoidable artefacts which may also include electrodermal and ocular activity. These are more pronounced in the waking state, with sleep recordings leading to more trustworthy data. Since intracranial ISA build-up can reach millivolt levels, scalp-recorded ISA build-up in hundreds of microvolts need not necessarily be regarded as an artefact if eye movements can be removed and contiguous channels are involved. The data also showed that a build-up can occur not only on the side of the epileptogenic process but also on the contralateral side, even when a structural lesion is present. Its clinical significance is as yet unknown. This aspect will require further study on a larger case material where long-term operative results from excision of epileptogenic tissue are available. The findings do, however, show that even when conventional filter settings are used, the display window should be opened to several minutes, rather than seconds, because a build-up of activity may become apparent under these circumstances. Opening the high-pass filter and decreasing the low-pass filter will allow the discharges to become even clearer and with downsampling, longer epochs can be studied.

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At present, the clinical significance of the episodic interictal ISA build-up is unknown. If it were indeed related to the epileptogenic process, it might suggest that even in 'localisation-related epilepsy' the dysfunction may be more widespread than one would assume from the conventional frequency band. If this were to be the case, it might explain to some extent why the results from surgical excision of the epileptogenic zone tend to decay when long follow-up periods are employed. This holds true even for temporal lobe seizures, which have the best surgical prognosis (Wieser et al., 2003; Yoon et al., 2003; De Tisi et al., 2011).

The major limitations of this study were twofold. For intracranial data only a relatively small area of the brain was sampled and usually unilaterally. This left wide gaps and since the ISA electrical field is more limited than for the conventional frequencies (Gumnit, 1961; Gumnit and Takahashi, 1965), important information may have been missed. While this is, in part, unavoidable, a more complete work-up of the previously scalp-recorded data, which includes the use of additional software above and beyond what the instrument manufacturer provides, might have been helpful because it could have made the placement of strips or grids more precise. In retrospect, some of the strips/grids might not have been placed optimally because the scalp data assessment had relied largely on the 10/20 system and the data were evaluated only on a routine clinical basis with the instrument manufacturer's software. The second major limitation pertains to scalp recordings because, as mentioned, only the sleep portions were fully trustworthy. However, even in sleep, the patients were quite restless with frequent shifts of position, which created artefacts and mainly the spindle and K-complex stages were recorded. To what extent this is a common feature of epilepsy patients with uncontrolled seizures is at present not clear and it will require further study. Furthermore, the scalp recordings had only limited electrode coverage, which also leaves the higher amplitudes in the infraorbital electrodes shown in Figs. 4 and 5 unexplained. They may have reflected ocular or orbitofrontal activity and additional electrodes would be needed to clarify this observation.

In conclusion, it can be stated that ISA is a normal part of the total EEG spectrum, but its assessment in normal individuals is still limited (Vanhatalo et al., 2004; Monto et al., 2008; Hughes and Lörincz, 2011; Picchioni et al., 2011). Further studies are indicated not only in epilepsy patients but also in those with other conditions. The physiological processes which underlie ISA are speculative at this time but astrocytic activity (Manning and Sontheimer, 1997; Parri et al., 2001; Amzica and Massimini, 2002; Benaroch, 2005; Amzica, 2006; Tian et al., 2005; Hughes and Lörincz, 2011), as well as blood barrier changes, have been suggested (Vanhatalo et al., 2004, 2005). Glial effects are of special interest because it has previously been shown, in a kindling experiment, that astrocyte swelling preceded neuronal changes (Rodin et al., 1979). Lehrmann et al. (2008) observed a similar phenomenon in measles-virus-infected mice with astrocytes and microglia showing the earliest changes. Inasmuch as glial discharges have been recorded with frequencies ranging from 0.003 to 0.1 Hz their contribution to ISA appears very likely (Hughes and Lörincz, 2011). Since the results, which were reported here readily, lend themselves to independent replication by other laboratories, it is hoped that these studies will soon be performed in order to shed further light on this important segment of the brain's electrical frequency spectrum.

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